

## RAT MODELS AND MICROSCOPY TECHNIQUES TO INVESTIGATE PATHOLOGICAL ASPECTS OF THE ACUTE *TRYPANOSOMA CRUZI* INFECTION

Fabrino, D.L.<sup>1,2</sup>; Leon, L.L.<sup>2</sup>; Genestra, M.<sup>2</sup> and Melo, R.C. N.<sup>1\*</sup>.

(1) Department of Biology, Federal University of Juiz de Fora, UFJF, Juiz de Fora, Minas Gerais, Brazil.  
[rossana.melo@ufjf.edu.br](mailto:rossana.melo@ufjf.edu.br)

(2) Laboratory of Biochemistry of Trypanosomatids, Oswaldo Cruz Institute, Rio de Janeiro, RJ, Brazil.

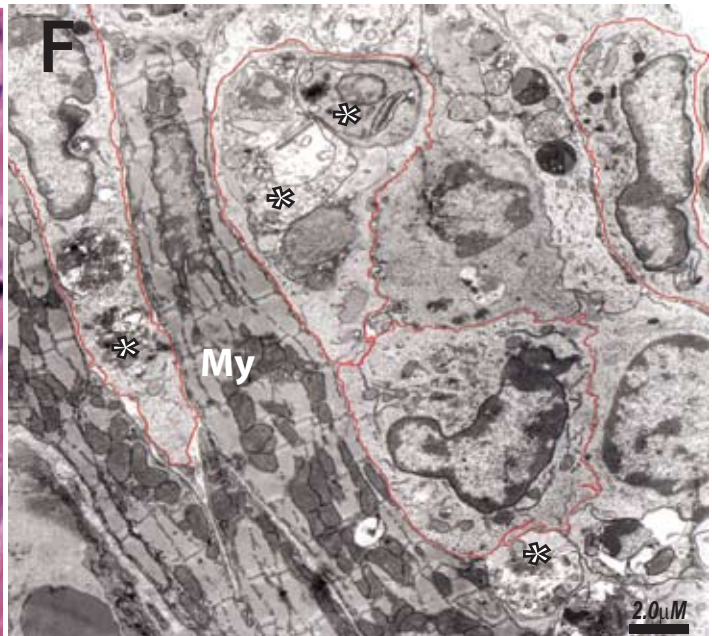
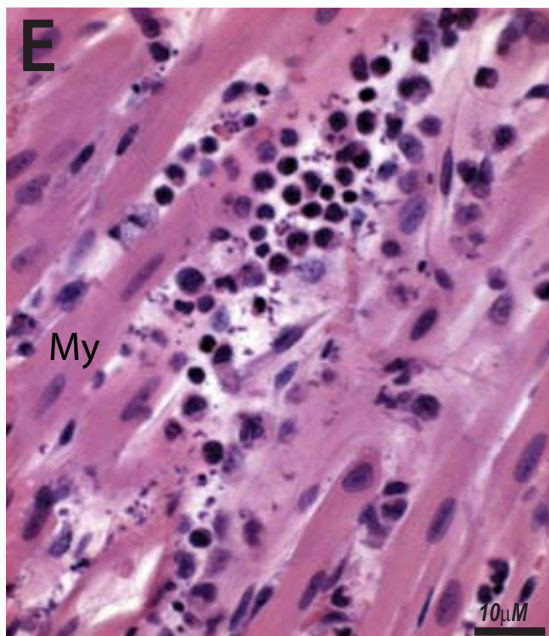
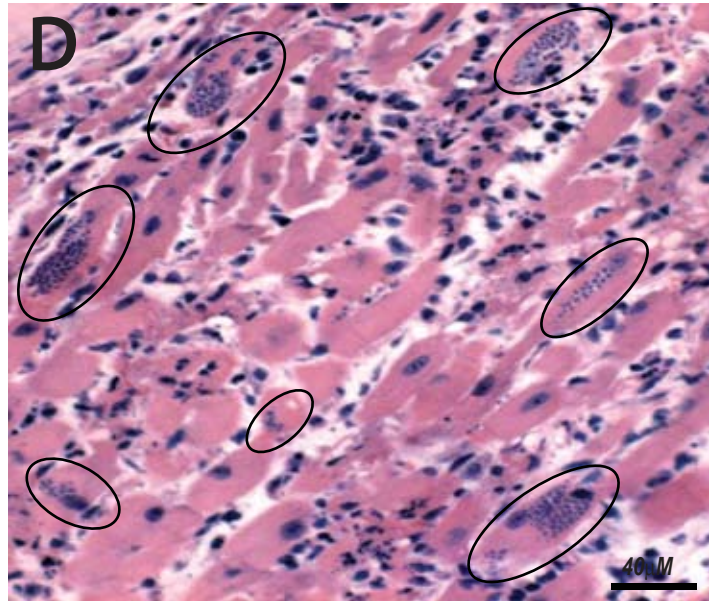
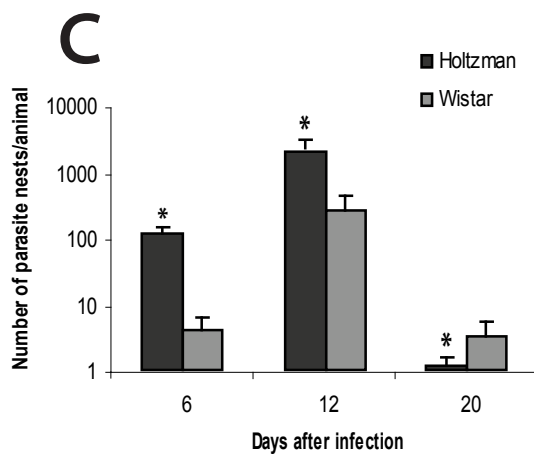
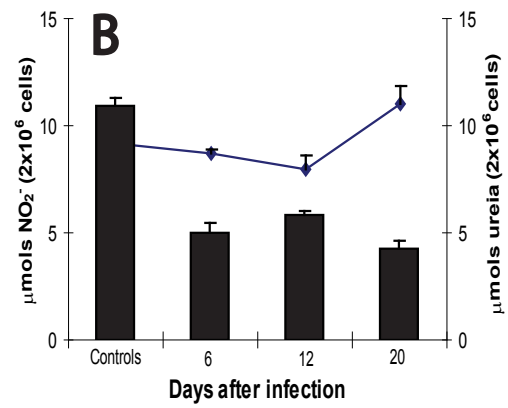
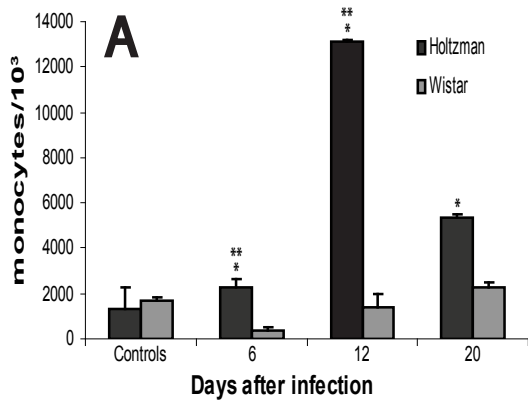
The protozoa *Trypanosoma cruzi* is the causal agent of Chagas' disease, one of the most important parasitic diseases of the Latin America. While different tools to manage the infection regard to detection and treatment have been discussed [1,2], biological research is still critical to understand basic aspects of the disease. Experimental *in vivo* studies, however, remain a key issue since they rely on animal models that have to mimic different features of the human infection. Here we have used two lineages of rats (Wistar and Holtzman) to comparatively evaluate the course of the acute infection, including the ability to infect the heart, the main *T. cruzi* target organ, and to mobilize monocytic lineage cells, which are crucial for parasite clearance and disease control [3,4]. Acute infection in both rat lineages was characterized by marked parasitemia, but these animals showed a distinct behavior to manage the infection. Quantitative histopathological analyses showed that while Holtzman rats induced a consistent heart parasitism, this aspect was not significant in Wistar rats. The infection in Holtzman, but not in Wistar rats, elicited a strong recruitment of peripheral blood monocytes in parallel to the increase of parasite load in the myocardium. A high number of inflammatory macrophages identified by transmission electron microscopy, exhibited morphological features of activation and directed parasite clearance in the heart. Interestingly, parasite killing was not related to the nitric oxide (NO) production by macrophages. On the contrary, NO levels were significantly inhibited by the parasite likely by an arginase-dependent mechanism. Our findings demonstrate differential response of Holtzman and Wistar rats to *T. cruzi*, and highlight the use of Holtzman rats as useful models to study different aspects of the monocyte/macrophage system during the acute infection. A better understanding of the monocyte/macrophage responses to the *T. cruzi* is central for the development of appropriate therapeutic interventions and Chagas' disease control. Supported by CNPq and FAPEMIG.

[1] Coura J.R. Mem Inst Oswaldo Cruz 2007 102 Suppl 1 113-22.

[2] Schofield CJ, Jannin J, Salvatella R. The future of Chagas disease control. Trends Parasitol 2006; 22(12):583-588.

[3] Fabrino D., Leon L., Parreira G, Genestra M, Almeida P., Melo R.C.N. Nitric Oxide 2004 11 (2): 166-74.

[4] Melo R.C.N. J Cell Mol Med 13 (2): 279-94, 2009.



**FIG.1: Different aspects of the acute *Trypanosoma cruzi* infection in rat models.** (A) High mobilization of peripheral blood monocytes (PBM) is observed in Holtzman rats; these cells increased in number at day 6 compared to control values. At day 12, PBM dramatically increased in comparison to numbers found at day 6 (\*) while at day 20, they decreased compared to day 12 (\*\*). (B) The acute infection did not induce nitric oxide production, but increased the levels of arginase by splenic macrophages. (C-F) Accentuated heart parasitism is seen in Holtzman rats in conjunction with mononuclear myocarditis, dissociated myocardial fibers (My) and degenerating parasite amastigote forms (\*). Samples analyzed at day 12 of infection. Data are expressed as mean  $\pm$  SEM and are representative of 3 independent experiments. 4-6 rats/group ( $P < 0.05$ ).